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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,172	12/03/2003	Amine Abina	034253-002	5982

21839 7590 03/09/2007

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,172	ABINA, AMINE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *27-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction requirement received on 12/5/06 has been entered. Applicant's election with traverse of Group I, and the species adenovirus as the first virus, adeno-associated virus as the second/additional virus, interleukins as the first heterologous protein and lymphokines as the second/additional heterologous protein encoded by the second/additional nucleic acid is acknowledged. Claims 1-37 are pending in the instant application. Based on applicant's elections, claims 27-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/5/06. Claims 1-26 are currently under examination. An action on the merits follows.

Election/Restrictions

As noted above, the applicant has elected Group I, and the species adenovirus as the first virus, adeno-associated virus as the second virus, interleukins as the first heterologous protein and lymphokines as the second/additional heterologous protein encoded by the second/additional nucleic acid, with traverse. The traversal is to the restriction between Groups I and II is based on applicant's argument that the groups are closely related and that both inventions can be searched simultaneously without serious burden on the examiner. The traversal is not found persuasive as the methods of Invention I and the methods of Invention II would require the use of different

search as the methods of Invention II involve the use of two different mammals versus the methods of Invention I which take place in a single mammal. Further, Invention II involves a step of repeated administration of the various viruses/nucleic acids in order to determine a specific amount of heterologous protein and virus that can i) trigger and immune response, and/or ii) trigger an immune response sufficient to deplete antigen presenting cells, and/or iii) an mount of virus that suppresses anti-heterologous protein immune responses in the mammal. None of these steps are required for the methods of Invention I. Thus, the search for invention I is clearly no co-extensive with the search for invention II. Further, based on the substantial differences in the methods steps of both inventions, it would place a serious burden on the examiner to search and examine both inventions together.

Thus, the restriction requirement is still deemed proper and is therefore made FINAL.

Regarding the election of species requirement, the applicant has not presented any arguments traversing the grounds for election of species. Instead the applicant requests that the examiner consider "cytokine" instead of "interleukins" as the first heterologous protein. While the claims do not recite "cytokine(s)", the specification does provide support for cytokines, which include the subgroup of interleukins, as the first heterologous protein. As such, applicant's request is granted and the election of "cytokine" as the first heterologous protein is acknowledged. It is further noted that the election of species requirement for the "second /additional heterologous protein" is withdrawn for the elected invention, Group I because a careful review of the claims reveals that the additional nucleic acid encoding the heterologous

protein of claim 11 and the heterologous protein of claim 12 are the same heterologous protein referred to in claim 1.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 10/25/04 and 1/21/05 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner and initialed copies of the 1449s are attached to this action.

However, please note that the listing of references on pages 39-40 of the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 11, and 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the method of claim 3 wherein the adenovirus is selected from a group that includes fragments or a wild type or recombinant adenovirus. A fragment of a virus is no longer considered a virus. As such, the recitation that a fragment of an adenovirus can be administered conflicts with the limitation in the parent independent claim 1 which recites that a "virus" is administered, not a portion or part of a virus. Therefore, the metes and bounds of the claim cannot be determined.

Claims 11 depends on claim 1 and recites the further administering of "an additional nucleic acid sequence encoding the heterologous protein, wherein the additional nucleic acid sequence is the same as or different than the nucleic acid sequence". From the phrase "the heterologous protein", it appears that the heterologous protein is the one recited in claim 1. Likewise, "the nucleic acid sequence" appears to refer to the nucleic acid recited in claim 1. As such, the metes and bounds of the additional nucleic acid sequence which is different that the nucleic acid sequence of claim 1 are not clear. Both must encode the same heterologous protein, so it is unclear how they are different. Clarification is requested.

Claims 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19 recite a method comprising a step of administering a recombinant virus to a mammal and "optionally" administering a virus that does not express the heterologous protein. The use of the term "optionally" renders the claims indefinite as it is unclear whether the

second step of administering a virus that does not express a heterologous protein is part of the method or not.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The applicant claims methods of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising co-administering to the mammal a virus in an amount sufficient to deplete or inhibit at least some antigen presenting cells of the mammal and a nucleic acid sequence encoding the heterologous protein, where the virus is administered either prior to or simultaneously with the nucleic acid. Dependent claims further limit the method to wherein the virus is a recombinant virus that encodes the heterologous protein, or recite that the method comprises an additional step where an additional virus, or an additional nucleic acid sequence encoding the heterologous protein, or the heterologous protein itself is administered to the mammal. As noted above, examination of the instant claims has been based on the elected species of "adenovirus" as the first virus, "cytokine" as the heterologous protein, and "adeno-associated virus" as the second/additional virus. The specification fails to provide an enabling disclosure for inhibiting the formation of neutralizing antibodies against a cytokine by

administering a recombinant adenovirus which encodes a cytokine, or by administering a wild type adenovirus or a recombinant adenovirus encoding a cytokine prior to or simultaneously with a recombinant adeno-associated virus encoding the same cytokine.

The specification teaches the desirability of using recombinant viruses as gene therapy vectors for treatment of disease, particularly hereditary diseases. However, the specification teaches that the formation of neutralizing antibodies against viruses such as recombinant adenoviruses, including antibodies against the adenovirus itself and antibodies against a heterologous protein encoded by the recombinant adenovirus, result in transient expression of the encoded therapeutic protein. The specification discloses that inhibition of neutralizing antibody formation would improve heterologous protein expression from the recombinant viruses presumably leading to improved therapeutic results. It is noted that the specification, while broadly using the term viruses, is primarily drawn to the use of recombinant adenoviruses. The specification provides minimal disclosure of other viruses such as adeno-associated viruses. Further, the working examples are all limited to the administration of single doses of a recombinant adenovirus encoding TPO or in one example recombinant adenovirus encoding beta-galactosidase using retro-orbital injection. Also, other than generally suggesting a two step method of administering an adenovirus followed by administration of a nucleic acid encoding a heterologous protein, the specification provides little guidance for the methods as claimed where more than one virus are administered.

Regarding the working examples, the specification discloses that the amount of recombinant adenovirus encoding a heterologous protein administered to a mammal determines whether it induces immunization or tolerization. The working examples, however, clearly

demonstrate that there is no specific dose of adenovirus that is always "tolerizing" rather than "immunizing". The working examples show that different preparations of the same recombinant adenovirus, an adenovirus encoding human TPO (Ad-TPO), require the administration of different amounts of the virus to inhibit neutralizing antibody formation against TPO. In one set of experiments, 6 X 10-9 pfu of Ad-TPO administered retro-orbitally to mice is immunizing and 8X10-9 pfu is tolerizing, whereas in a second set of experiments 6X 10-9 pfu of Ad-TPO is tolerizing. It is further noted that the specification is silent as to whether neutralizing antibodies against adenoviral protein were also inhibited as the "tolerizing" dose. The working examples also teach that a second recombinant vector encoding beta-galactosidase required the higher amount of 8X10-9 pfu for a "tolerizing dose". However, this experiment only states that "some" hepatocytes showed beta-gal expression after 5 months. It is unclear from these results whether neutralizing antibodies against beta-gal were in fact inhibited. Further, the specification acknowledges the unpredictable variability of the "tolerizing dose" stating that the tolerizing dose must be independently determined for each viral preparation. It is noted that the working examples do not demonstrate the separate administration of a wild-type adenovirus and a separate nucleic acid encoding TPO or beta-gal such as an adeno-associated virus encoding TPO either simultaneously to the same site, or separated by time and/or location. The working examples also do not utilize any route of injection other than retro-orbital injection, an intravenous delivery route. In addition, please note for claim 26 that the amount of adenovirus claimed, 4X10-9 or greater clearly encompasses amounts that are not effective as evidenced by the working examples. Further, it is unclear how the amount of particles claimed in claims 24-25 correspond to the pfus of virus administered in the working examples.

At the time of filing, the administration of recombinant adenovirus for expressing encoded heterologous proteins in mammals was well known and well documented, as were the associated problems with recombinant adenovirus administration, such as the development of neutralizing antibodies against both adenoviral proteins and heterologous proteins encoded by recombinant adenoviruses. Abina et al. for examples provides a summary of the state of the prior art of neutralizing antibodies induced by recombinant adenoviruses and further provides a specific example which demonstrates that a single dose of 6X10-9 pfu of a recombinant adenovirus encoding human TPO administered intravenously to mice produces cross-reactive neutralizing antibodies against human TPO (Abina et al, (1998), see IDS of 4/8/04, pages 4481-4482). Further, numerous prior art publications teach the use of recombinant adenovirus for at least transient expression of heterologous proteins, including cytokines, see for example U.S. Patent 6,399,587 (2002), Mehtali et al. which teaches adenoviruses encoding human IL-2 and the administration of recombinant adenovirus to mammals in dosages of between 10-6 and 10-12 pfu; however, none teach that "high" doses of recombinant adenovirus are capable of inhibiting formation of neutralizing antibodies against a heterologous protein encoded by the recombinant adenovirus or administered separately in a different viral vector or as a soluble protein.

Based on the above, the specification fails to provide sufficient guidance for the breadth of the claims as written. The claims are drawn broadly to the administration of either wild type or recombinant adenovirus by any route of administration in "an amount sufficient to inhibit or deplete at least some antigen presenting cells". The claims further encompass where the heterologous protein is encoded by the recombinant adenovirus or by a separate nucleic acid, such as a recombinant adeno-associated virus comprising a nucleic acid encoding a cytokine, and

where the adenovirus and the nucleic acid are administered at the same time to different sites, or to the same or different sites at different times. However, in view of the state of the prior art of adenoviruses and recombinant adenoviruses, which did not teach or suggest the ability of wild type or recombinant adenovirus to inhibit formation of neutralizing antibodies, the limited disclosure in the specification and specifically the working examples fails to overcome the high level of unpredictability in using adenovirus to "tolerize" a mammal against the expression of a heterologous protein such as a heterologous cytokine. As discussed in detail above, the working examples demonstrate the unpredictability in determining the "tolerizing dose" of recombinant adenovirus encoding the heterologous protein *a priori*, even between different batches of the same virus. This unpredictability in achieving tolerance versus immunization is further increased by the limitation of the working examples to a single route of administration, intravenous, and by the use of a single recombinant vector which encodes the heterologous protein. In view of the large body of work in the prior art using both wild type and recombinant adenoviruses, where neutralizing antibodies were formed over a large range of doses and using different routes of administration, the skilled artisan would not have been able to predict without undue experimentation whether the applicant's successful demonstration of transient tolerance with a single recombinant adenovirus, at a dosage in one experiment which the prior art teaches to be immunizing not tolerizing, could be extrapolated to any recombinant adenovirus encoding any cytokine and any route of administration, or to the administration of separate adenovirus and nucleic acid encoding the cytokine, either simultaneously or not, using any route or routes of administration. As such, in view of the state of the art of adenovirus induction of neutralizing antibodies at the time of filing, the breadth of the claims, the limited disclosure in the

specification and working examples, and the unpredictability as demonstrated by both the prior art and the working examples for using adenovirus to inhibit rather than induce neutralizing antibodies, it would have required undue experimentation to practice the invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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PRIMARY EXAMINER